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EXAMINER	
MCKENZIE, THOMAS C	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 05/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/898,809	RAJAGOPALAN ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-14 and 23-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-14 and 23-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to amendments filed on 3/16/04. Applicant has not amended any claims. Applicants have canceled claims 1, 2, and 11. Claims 32 and 33 are new. Claims 12-14 and 23-33 are use claims. This is the fifth action on the merits. The application concerns some uses of cyanine dye compositions.

Response to Amendment

2. Applicants' cancellation of composition claims 1, 2, and 11 renders moot the indefiniteness rejection made in points #11 and #12 of the previous office action. Applicants' new claim 32 contains the limitation "wherein E is a target binding unit that is recognized by and binds to a target site on the tissue". While this does not have literal support in the specification, Fig. 1 teaches that E is a target binding unit and the curved arrow is art-recognized in chemistry as indicative of interaction with and binding to the "target tissue". Thus, claim 32 does not introduce new matter.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-14, 23-31 remain rejected and claim 33 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrases "somatostatin receptor binding molecule" ... "carbohydrate receptor binding molecule" are all indefinite for two reasons. "E" cannot be a molecule, which lacks any free valence; it must be a univalent radical.

4. Secondly, what are the chemical structures of these fragments that define radical "E"? These are not art-recognized structural terms. The passage spanning line 17, page 12 to line 12, page 13 lists the function that these radicals are to perform, but does not clarify the molecular structures intended. Applicants' statement that "E" is an epitope only further clouds the issue. The Examiner understands that an epitope is a portion of a macromolecule chain capable of forming an antibody. Is "E" an antibody or only a short peptide segment from an antibody? If only macromolecules can be epitopes, then how can steroid hormones and amino acids be epitopes? Are the synthetic biomolecules listed in lines 11-13, page 13 "E"?

5. Claims 12-14 and 23-31 remain rejected and claim 33 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specific phrase "carbohydrate receptor-binding molecule" is indefinite. There is an entire class of such carbohydrate receptors, quite possibly thousands, and generally poorly understood and characterized. How

would one know if any molecule E bound to such a receptor without checking all such receptors?

These three indefiniteness rejections will be considered together. Applicants simply assert that the claims are definite but offer no evidence. Where are the textbook passages or review articles that would allow the BS synthetic organic chemist to understand what structures for the radical E are being claimed using Applicants functional terms? Where are the assays, for example, that would allow her to determine if E binds to the thousands of "carbohydrate receptor[s]"? What exactly must bind to the somatostatin receptor to fit this definition? It cannot be "E" itself because "E" is a radical not a stable molecule. Is it E-H? Or some derivative like E-phenyl? How about some complex molecule like 2,4-diamino-6-phenyl-pyrimid-5-yl-E? What is only one of these hypothetical molecules, say E-phenyl, binds to the somatostatin receptor but the other three do not. Is radical E still included in Applicants' definition of a "somatostatin receptor binding molecule"? Somatostatin certainly binds to its receptor and contains a number of hydrogen radicals. Does an individual hydrogen radical meet the limitations of "E"?

6. Claim 32 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. The phrase, "E is a target binding unit that is recognized by and binds to a target site on the tissue" is indefinite. What is the structure of this radical? What targets and which tissues are intended?

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-14 and 23-31 remain rejected and claims 32 and 33 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preparing compounds with radical "E" being dihydroxyindolecarboxylic acid or the peptide Cytate, does not reasonably provide enablement for preparing all the other functionally described E binding molecules. The specification does not enable any person skilled in the art of organic synthesis to make the invention commensurate in scope with these claims.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims." *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*,

230 USPQ 546. The issue is synthesizing compounds whose structures are not known.

a) If E is an epitope from an antibody, raising all possible antibodies to the somatostatin receptor and locating all the possible epitope sites on these antibodies is an impossible task. Alternatively, screening all "hormones, amino acids, peptides, ... and aptamers" to determine if they bind to the receptors listed in claim 1 is an open-ended and potentially inconclusive research project. Locating the epitope on any particular antibody to a somatostatin receptor say, would a moderate degree of experimentation. However, all possible antibodies would have to be made because the individual epitope sites would differ. After this is done, each individual radical would have to be synthesized in a form that would allow attachment to the rest of the pictured molecule. Thus, the quantity of experimentation required is huge. b) The direction concerning the compounds claimed is found in Figure 2. In that figure, the radical "E" is described as "Biomolecule". Thus, Figure 2 does not appear to be a working example. There is neither direction given concerning the synthesis of "biomolecule" nor its attachment to the rest of the claimed formula. c) There are no working examples of a compound of formula given in claim 1. There is no procedure given to determine the affinity of any substance to the receptors listed in claim 1. d) The

nature of the invention is chemical synthesis, which involves chemical reactions. e) The state of the art for tumor binding agents is given in the references spanning line 22, page 13 to line 5, page 14. The state of the art is that even complete directions to a team of pharmacologist, enzymologists, and immunologists to search for radical "E", hardy constitute direct to the chemist of how to make these substances. f) The artisan using Applicants invention to prepare the compounds whose use is claimed would be a process chemist or pilot plant operator with a BS degree in chemistry and several years of experience. g) Chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. h) The breadth of the claims includes all the presently unknown list of functionally described radicals E embraced by claim 1. Reference AR teaches the use of an octapeptide which binds to the somatostatin receptor. A radical which derived from this peptide would fit the definition of "E" but is unclear if there additional such peptides or how the peptide Cytate was identified. The scope of the claimed subjected matter, as far as the "E" radical, is enormous.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue

experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Applicants make no arguments concerning this rejection but simply assert that they are enabled for making all of these unknown molecules. How that is possible when synthetic procedures the process chemist would need are left unsaid?

8. Claims 12-14 and 23-31 remain rejected and claims 32 and 33 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way to convey reasonably to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The issues concerning the meaning of phrases "somatostatin receptor binding molecule" ... "carbohydrate receptor binding molecule" and "E is a target binding unit that is recognized by and binds to a target site on the tissue" are discussed above. Claims 12 and 32 do not contain a complete generic formula.

According to the MPEP §2163 I. A. "the issue of a lack of adequate written description may arise even for an original claim when an aspect of the claimed

invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention. The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art." The MPEP states in §2163 II 3 ii) "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406." Applicants have disclosed no species and have made no assertion that there is any correlation between the biological function of radical "E" and its structure.

As discussed above the phrase ""somatostatin receptor binding molecule" ... "carbohydrate receptor binding molecule" and "E is a target binding unit that is recognized by and binds to a target site on the tissue" are not art recognized in

medicinal chemistry. According to the MPEP §2163.02 Standard for Determining Compliance With the Written Description Requirement,

> "The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed". *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter". *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In *re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983))."

Thus, the chemist of ordinary skill in the art, who would make Applicants' compounds, would not know what "somatostatin receptor binding molecule" ... "carbohydrate receptor binding molecule" and "E is a target binding unit that is recognized by and binds to a target site on the tissue" were. That chemist would not have understood the inventor to be in possession of the claimed compounds at the time of filing.

This case was filed before Applicants had a clear idea of the structures of their desired compounds, how to make their compounds, and use them. The

specification provides broad areas of future research and speculation, inviting undue experimentation in learning how to use Applicants' invention. Applicants may well now be developing practical applications of their photosensitizers, but the question here is what application they possessed at the time of filing. Anything is possible but as the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences wrote in *Bindra v. Kelly*, 206 USPQ 570 "*Probable* utility does not establish practical utility. Practical utility can, in our view, be established only by actual testing therefore, or by establishing such facts as would be convincing that such utility could be "foretold with certainty." *Blicke v. Treves*, supra, 112 USPQ at 475."

Applicants are reminded of what the U.S. Court of Appeals Federal Circuit wrote in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398, "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See *Fiers*, 984 F.2d at 1169-71, 25 USPQ2d at

1605-06 (discussing Amgen). "It is only a definition of a useful result rather than a definition of what achieves that result." "The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.")".

Applicants assert that the rejected claims meet the written description requirement. However, assertion is not evidence. Where is the evidence of any known or disclosed correlation between functional language and structure, as required by *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406?

9. Claims 12-14 and 23-31 remain rejected and claim 32 and 33 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating any "target tissue" or treating any human disease. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. The factors to be considered in making an enablement rejection have been summarized

above. The issues are the complete lack of any biological assays, the broad scope of the diseases to be treated, and the lack of guidance as to how tumors located within the body are to be treated by light.

a) Determining if any particular claimed compound would treat any particular target tissue disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large quantity of experimentation. b) The direction concerning treating diseases is found in the passage spanning line 10, page 8 to line 7, page 9, which merely states Applicants' intention to do so. In lines 14-16, page 2, line 18, page 2, and the lines spanning line 22, page 2 to line 2, page 3 Applicants discuss specific diseases amenable to photo therapy.

Applicants describe formulations in the passages spanning line 11, page 16 to line 2, page 17 and line 17, page 17 to line 5, page 18. There is no working example of any formulation required to practice Applicants intended therapies. Doses required to practice their invention are described in lines 2 and 3, page 17. A 5,000-fold range of doses is recommended. Since no cyanine dye linked to the mercaptooxy-aryl radical of the formula in claim 1, has ever been used to treat any

human disease, how is the skilled physician to know what dose to use for each of these different diseases? There are no biological assays described anywhere in the specification. There is no biological data of any sort for any of Applicants' compositions or compounds. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts in photo therapy of human diseases is found in the passage spanning line 7, page 2 to line 2, page 3 of the specification. It is simply illogical that prostate, lung, colorectal, and brain tumors could be treated by phototherapy. What would be the source of light on these organs located inside the body cavity?

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the millions of compounds of claim 1 as well as the hundred of diseases embraced by the term "target tissue". Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

See *Ex parte Powers*, 200 USPQ 925 concerning the type of testing needed to support *in vivo* use claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

Applicants argue that phase II clinical trials are not required for enablement for therapy claims. Applicants also point to an endoscope as a possible light source for treating tumors located within the body cavity. This is not persuasive. As to the first point, the Examiner made no such requirement concerning clinical trials. What is required is evidence of correlation between biological assays and the efficacy for the claimed therapy. In the present case there are no assays at all. In a case which is factually similar to the present application in that no biological testing data was revealed, *Ex parte Bhide* 42 USPQ2d 1441, the Board of Patent

Appeals and Interferences wrote "[w]hile in *vitro* or in *vivo* tests would not be the only possible way to overcome our basis for questioning applicants' utility, in *vitro* or in *vivo* tests certainly would provide relevant evidence". The issue in the present case is not the utility of applicants' compounds, which was at issue in *Ex parte Bhide* 42 USPQ2d 1441, but rather the narrower issue of enablement for claims drawn to the treatment of all claimed therapies. Since such a claim is inherently not credible, the standard of proof required for such an assertion must be high.

Concerning the second point, an endoscope is used to view and illuminate the inside of the GI tract. While it might be possible to illuminate a colorectal tumor with an endoscope, it would be impossible to illuminate a brain tumor. The prostate gland is a body, surrounding the beginning of the urethra in the male. Since the prostate is outside the urethra, a light inserted inside the urethra would not be able to illuminate any such tumor. The lung contains bronchi, which branch into smaller tubes, called secondary bronchi, which branch again into still smaller tubes called bronchioles, and finally end in the grapelike clusters of alveolar sacs. Lung cancer occurring in such small tubes and sacs is inaccessible to the bronchoscope, which is the lung analog of Applicants proposed endoscope.

10. Claim 31 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The list of diseases that Applicants intend to treat is taken from lines 1-9, page 13. This passage of the specification does not deal with disease treatment but rather is part of the functional definition of radical "E". There is insufficient nexus between this structural definition on page 13 and disease treatment. The passages dealing with intended disease treatment were described above in the enablement rejection.

Applicants make no argument concerning this rejection.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire

on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

13. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts

to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK/me